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ANIMAL STUDIES OF LIFE SHORTENING AND CANCER RISK FROM SPACE RADIATION

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ABSTRACT

The U. S. Air Force study of the delayed effects of single, total body exposures to simulated space radiation in rhesus monkeys is now in its 21st year. Observations on 301 irradiated and 57 age-matched control animals indicate that life expectancy loss from exposure to protons in the energy range encountered in the Van Allen belts and solar proton events can be expressed as a logarithmic function of the dose. The primary causes of life shortening are cancer and endometriosis (an abnormal proliferation of the lining of the uterus in females). Life shortening estimates permit comparison of the risk associated with space radiation exposures to be compared with that of other occupational and environmental hazards, thereby facilitating risk/benefit decisions in the planning and operational phases of manned space missions. Calculations of the relative risk of fatal cancers in the irradiated subjects reveal that the total body surface dose required to double the risk of death from cancer over a 20-year post exposure period varies with the linear energy transfer (LET) of the radiation. The ability to determine the integrated dose and LET spectrum in space radiation exposures of humans is, therefore, critical to the assessment of lifetime cancer risk. (Reprints)

INTRODUCTION

The study of the lifetime effects of space radiation on rhesus monkeys--a study initiated in 1964 and still in progress at the School of Aerospace Medicine--remains the sole source of controlled experimental data on the lifetime effects of total body proton irradiation in a long-lived animal species. Adolescent rhesus monkeys of similar age and both sexes were exposed to single, total body doses of one of several types and energies of radiation, including protons, electrons, and X-rays (Table 1).

TABLE 1 Simulated space radiation exposures in rhesus monkeys

TYPE	ENERGY (MEV)	DOSE RANGE (RAD)	DATE	MALES	FEMALES
PROTON	32	280-560	JUL 64	6	6
PROTON	55	25-600	APR 65	50	22
PROTON	138	210-650	JAN 65	19	13
PROTON	400	50-600	MAR 65	28	27
PROTON	2300	56-560	OCT 65	21	25
X-RAY	2	446-716	MAR 64	15	17
ELECTRON	2	900-1500	NOV 69	5	7
ELECTRON	1.6	1000-1500	MAY 68	12	0
PROTON	10 & 100 (9:1)	300-1200	APR 69	17	11

Of particular importance are the protons, which represent the most significant hazard in solar particle events. The availability of controlled data on proton irradiation in a primate is valuable in quantifying human risk, because previously published estimates have been derived from populations exposed to other types of radiation which are not directly

applicable to risks from corresponding doses of proton irradiation. Conversion of nuclear weapon exposure data to space radiation risk estimates requires the use of estimated quality factors to correct for the relative biological effectiveness of the radiations involved. The simulation of space radiation theoretically eliminates the requirement for a quality factor, and the non-human primate model reduces the uncertainty of extrapolation of the animal data to humans. The exposure conditions have been described in other reports [1-7].

The data upon which our estimates are based are compiled from continuous observations on 304 irradiated animals and 57 age-matched nonirradiated controls. The existence of a relatively large control population permits estimates of the life expectancy loss and relative risk of harmful effects associated with single exposures to various doses of each type of space radiation. The precision of these estimates is often low, because of small initial populations in some groups; but, over a 20-year interval, some significant findings have emerged.

LIFE EXPECTANCY LOSS

Loss of life expectancy is a common parameter by which the risk associated with hazardous activity is evaluated. Individual risk factors with identical life expectancy loss may not have the same acceptability due to other considerations, but life expectancy reduction is a helpful criterion in making risk/benefit decisions for operations in a hazardous environment. Illustrated in Figure 1 is the survival probability of the control and irradiated populations of monkeys over a 20-year period. The irradiated subjects are dying faster than the controls and their curve falls below the 95% confidence interval of the controls at approximately 11 years post-irradiation.

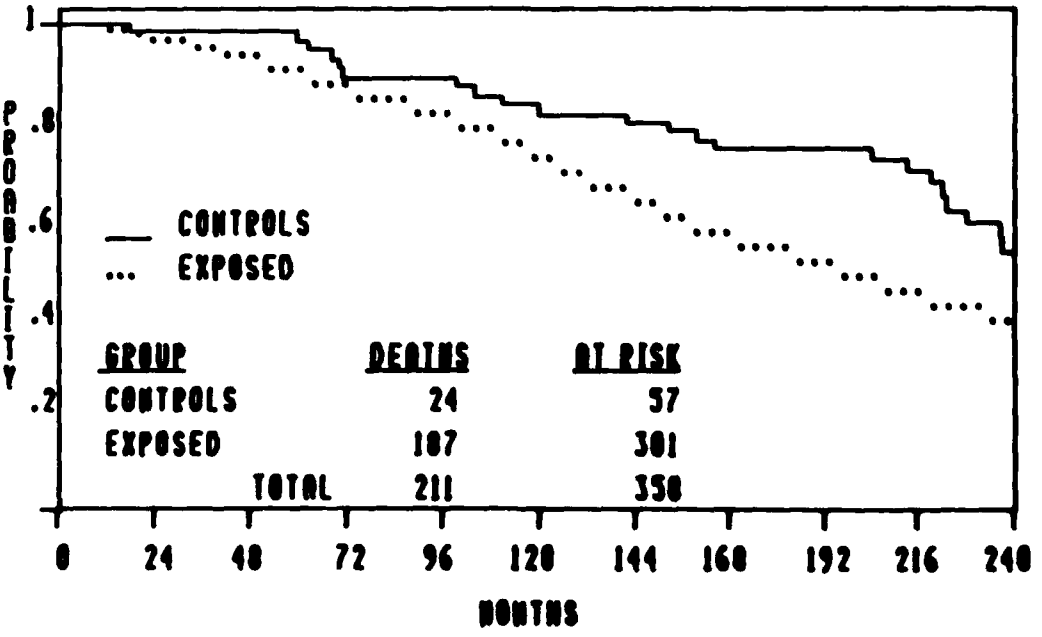

Fig. 1. Kaplan-Meier survival probability of monkeys exposed to simulated space radiation. Nonirradiated controls are age-matched

Estimates of the loss of life expectancy, calculated by the Cohen-Lee method /10/, have been computed for a 20-year post-irradiation interval. The Cohen-Lee formula for estimating life expectancy loss from a single factor uses the death rate from all factors in a reference population as its basis of comparison. To normalize data from reference populations that have different average life spans, such as monkeys and humans, a correction factor based on the ratio of the average life expectancies of the two populations may be used. For monkey-to-human conversions, the factor is 2.5, based on a human/monkey life expectancy ratio of 75/30. Data on the prompt effects of ionizing radiation, particularly LD_{50} studies on rhesus monkeys /8/, suggest that the two species do have similar dose-response relationships. An exception may be endometriosis, which has been a major cause of mortality in the female monkeys /11/. Since endometriosis is not normally a life-threatening conditions in humans, separate estimates excluding the contribution of endometriosis

were calculated. Life expectancy loss associated with proton dose and energy is shown in Figures 2 and 3. Calculations are relative to 32-2300 MeV controls in Figures 2-7, Figures 8-10 additionally include 2 MeV X-rays and endometriosis in Figure 8 is relative to all female controls.

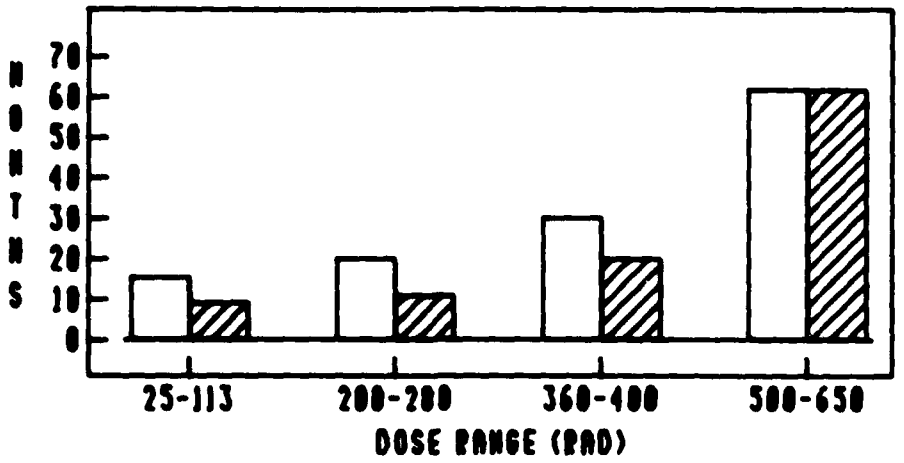

Fig. 2. Life expectancy loss based on mortality in the 20-year post-irradiation period in monkeys exposed to protons. Dose ranges include all proton energies. Open bars include all causes of death. Shaded bars exclude endometriosis.

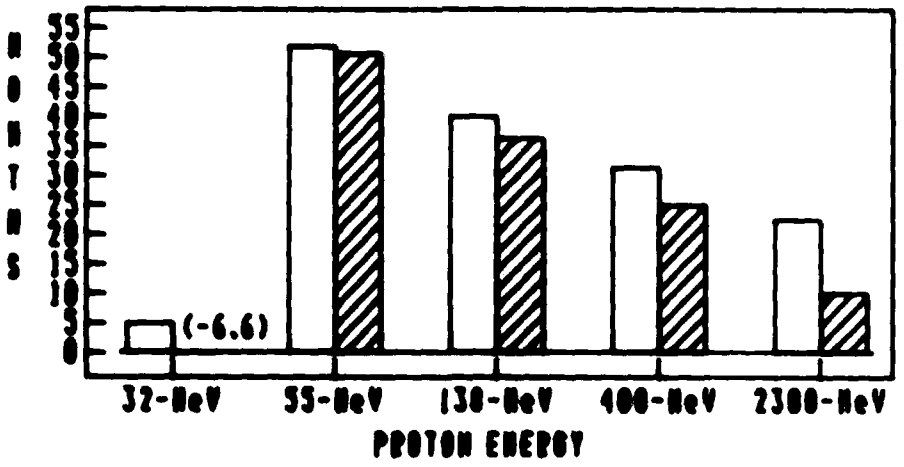

Fig. 3. Life expectancy loss related to energy in the proton exposed monkeys. Energy groups contain all dose ranges. Shaded bars exclude endometriosis as a cause of death.

The greatest loss associated with energy occurred in the mid-range, particularly in the 55-MeV group. As expected, the life expectancy loss was directly related to the total body dose. The combined effect of dose and energy is illustrated in Figure 4. The results reflect the greater biological effectiveness of the 55-MeV protons with the low energy-high dose combination resulting in a 73-month or 31% life expectancy loss for a 20-year post-irradiation period.

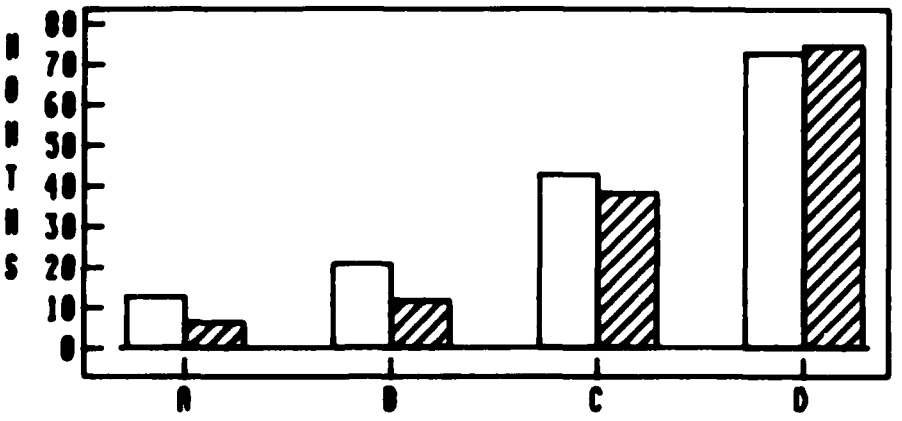

Fig. 4. Life expectancy loss over a 20-year interval related to both dose and energy. Group A: 32-55 MeV, 25-280 rad. Group B: 138-2300 MeV, 25-280 rad. Group C: 138-2300 MeV, 360-800 rad. Group D: 32-55 MeV, 360-800 rad. Shaded bars exclude endometriosis as a cause of death.

The charts in Figure 5 show the primary causes of death in the irradiated and control populations. Neoproliferative disease, including tumors and endometriosis, account for a considerably greater fraction of the total deaths in the irradiated animals than in the controls. Irradiated subjects also tend to have more fatal infections.

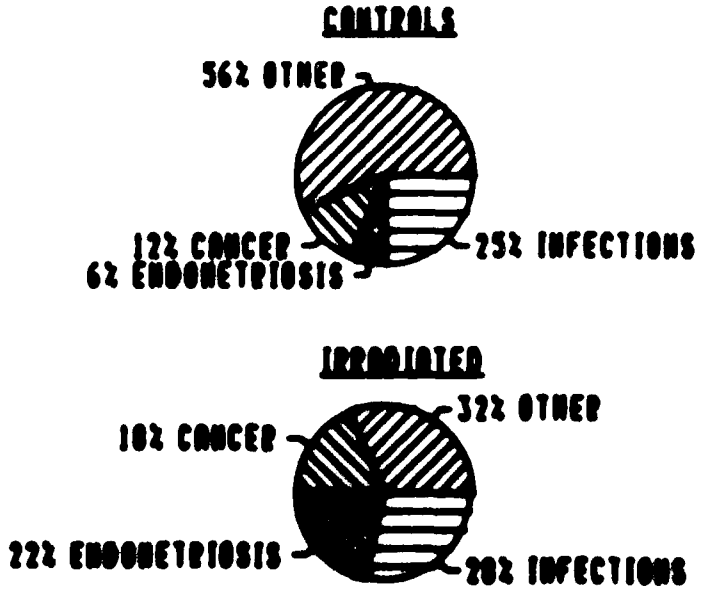

Fig. 5. Primary causes of mortality in control and irradiated monkey populations during 20-year post-irradiation period.

As demonstrated, in Figure 6 life expectancy loss from proton radiation, within the energy range encountered in space, can be fitted to an exponential curve.

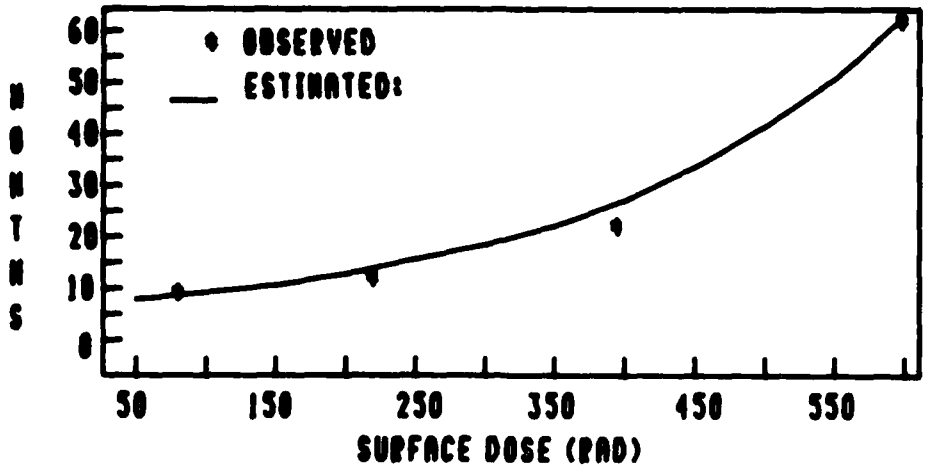

Fig. 6. Observed 20-year life expectancy loss (ignoring endometriosis) at four weighted mean doses doses of proton irradiation in monkeys. The curve of estimates is derived from least squares analysis. ($y=3.06e^{.0052x}$)

The calculated life expectancy loss per unit of radiation of all types is shown in Figure 7. This saddle-shaped curve can be used to estimate life shortening from the doses recorded by passive personal dosimeters where the type and energy of the radiation is undetermined. Note that for 55-MeV protons and 2-MeV X-rays the estimates are constants (3.6 and 1.7 days per rad).

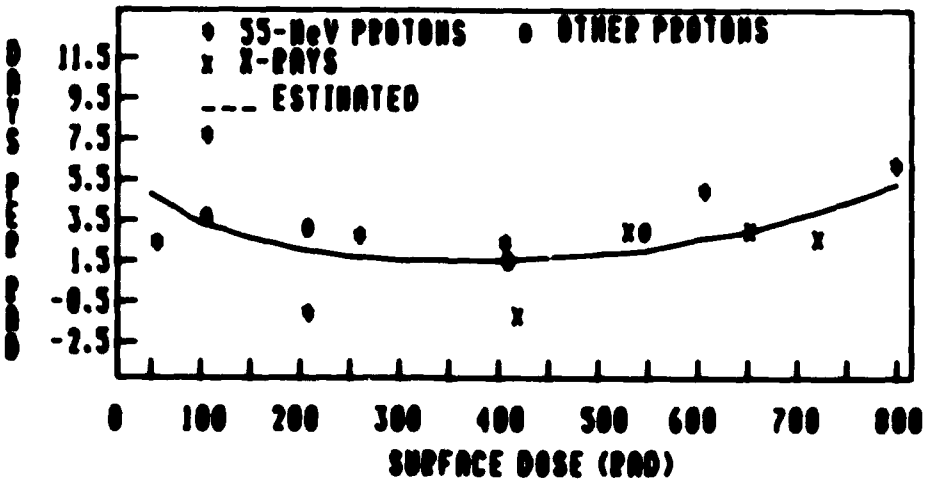

Fig. 7. Observed life expectancy loss (days per rad) from all types of experimental radiation in monkeys. The curve represents estimates calculated by least squares analysis. ($y=.000025\ x^2 - .02x + 5.2$)

RISK OF FATAL CANCER

Three control and 35 irradiated animals have died of cancer. This translates to an excess mortality of 2.15×10^{-6} fatal cancers per year rad. We have expressed annual relative risk as the ratio of the number of cases per monkey year in the irradiated versus control populations. A value of one indicates equality between the groups, while a value less than one indicates a lower incidence in the irradiated population. Because the number of years at risk is a random variable, the estimation of confidence limits for annual relative risk is a complex problem for which we do not yet have an answer. The relative risks for major causes of death are compared in Figure 8. The effect of dose and energy is again apparent. The combination of low energy and high dose results in the greatest relative risk for all major causes of death except endometriosis. The location of the uterus makes it vulnerable only to the deeply penetrating high energy radiations. The overall incidence of endometriosis in the irradiated animals is slightly more than 50%, including non-fatal cases, compared to 14% in the controls. As indicated in Figure 8, all dose groups had a greater susceptibility to endometriosis than the controls (Fischer's exact test, $p<.01$).

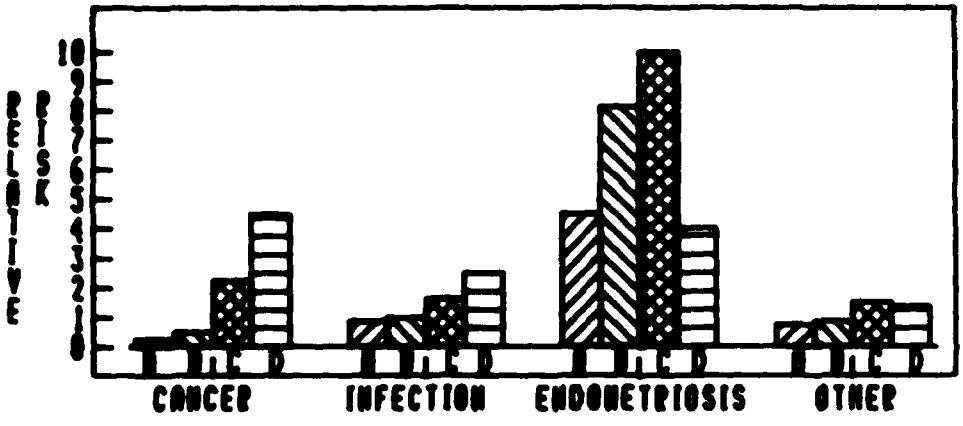

Fig. 8. Annual relative risk of death from major causes in four dose-energy combinations. Group A: 32-55 MeV, 25-280 rad. Group B: 138-2300 MeV, 25-280 rad. Group C: 138-2300 MeV, 360-800 rad. Group D: 32-55 MeV, 360-800 rad.

The relative risk of cancer death is also related to both dose and energy. The risk from high energy radiation is presented in Figure 9. The estimated dose to double the relative risk of fatal cancer is 342 rem, assuming a quality factor of 1.0 for conversion of rad to rem. Of greater interest is the risk associated with lower energy protons, which constitute the majority of the Van Allen Belt protons and solar flare particles.

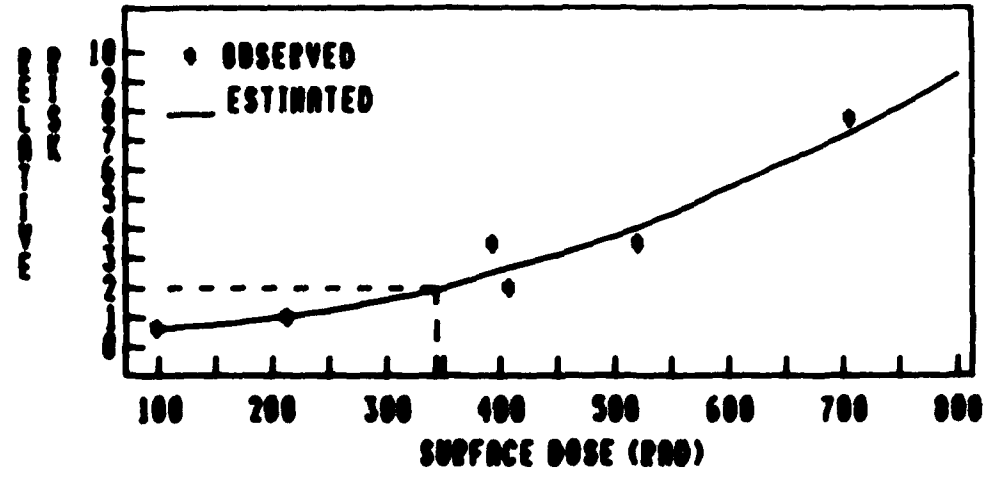

Fig. 9. Annual relative risk of fatal cancer observed at six weighted mean doses of low LET (138-2300 MeV proton or 2 MeV X-ray) radiation in monkeys. The curve of estimates fits a quadratic equation, ($y=.0000185x^2 + .0063x + .521$)

Observation of 72 animals, exposed to 55-MeV protons, revealed that the dose to double the cancer risk was 245 rad (Fig. 10). Although the rate of all cancers is significantly higher in the exposed subjects, only one type of cancer has occurred in sufficient numbers to suggest that it is associated with a particular type of radiation. Nine fatal brain cancers of similar morphology (Grade IV astrocytoma or glioblastoma multiforme) have occurred in the 55-MeV proton group.

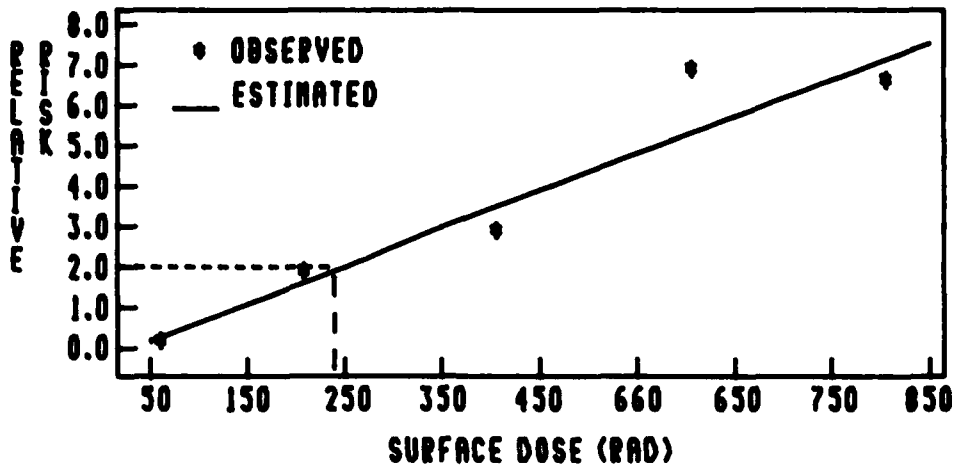

Fig. 10. Annual relative risk of fatal cancer observed at five weighted mean doses of high LET (55-MeV) proton irradiation in monkeys. The estimates best fit a linear equation. (y=.0092x - .266)

According to the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) /12/ radiation induced tumors, with the exception of leukemia, generally have mean latencies of 20 years or greater in the human. One might expect this to be proportionately less (35/70) in the monkey. Only one case of leukemia has occurred in the irradiated monkey population. This case was seen at 14 months post-irradiation in a male exposed to 100 rad of 400 MeV protons.

SAFETY CONSIDERATIONS

The 1970 dose limit tables for astronauts (Table 2) were based on a reference dose of 400 rem of total body, prompt (high dose rate) mixed neutron-gamma radiation from nuclear fission.

TABLE 2 1970 Space Science board recommendations for space radiation exposure limits /13/

CONSTRAINT	BONE MARROW	SKIN	LENS	TESTES
DAILY AVERAGE	.2 REM/DAY	.6 REM/DAY	.3 REM/DAY	.1 REM/DAY
30 day	25 REM	65 REM	37 REM	13 REM
QUARTERLY	35 REM	105 REM	52 REM	18 REM
YEARLY	75 REM	225 REM	112 REM	38 REM
CAREER	400 REM	1200 REM	600 REM	200 REM

Recently, the NCRP has suggested that the reference may be too high by a factor of at least two /14/. This is supported by our data on the relative risk of fatal cancers in monkeys exposed to simulated space radiation. Since the estimated doubling dose for fatal cancers from 55-MeV proton irradiation is 245 rad, total body surface dose, a cumulative career dose of 200 rem would seem to be a reasonable limit for non-emergency military operations. Although the net effect of exposure to all types of space radiation on cancer incidence and mortality appears to be little different from that of gamma radiation or X-rays, there is ample evidence of the greater biological effectiveness of certain components of the particulate radiation energy spectrum. The high incidence of brain tumors in monkeys exposed to 55-MeV protons is probably related to the energy distribution pattern of the particle in

the tissue. A proton with an incident energy of 55 MeV transfers all of its energy in the first 2.5 cm of soft tissue (Bragg effect); therefore, a large population of cells in the cerebral cortex is vulnerable during an isotropic (multi-directional) exposure in space. Radiation biologists regard cancer as a stochastic, or non-threshold effect. In other words, any exposure to 55-MeV protons can have an associated brain tumor risk, the magnitude of which may only be determined by carefully controlled dose-response studies. Accurate assessment of the human risk from space radiations of high biological effectiveness (such as Bragg effect protons) or heavy ions (such as stripped oxygen or iron nuclei) will require improvements in crew dosimetry to identify and integrate the separate components of the space radiation spectrum.

The increased risk of endometriosis in the irradiated female monkeys is an unusual finding in view of the absence of any reported correlation of this condition with radiation in human females. The lesion in monkeys does appear to be morphologically identical to that occurring spontaneously in humans, although it is seldom fatal in women. Since endometriosis would not have been classified as a cause of death in the atomic bomb casualty study, a relationship to irradiation would not have been detected in the mortality studies; however, any marked increase in endometriosis should be detected in the Adult Health Study of survivors. Additional work is required before our observations on monkeys can be interpreted as indicating increased human risk. Little is known about the relative radiosensitivity of monkey and human endometrial cells, or how age and hormonal state might affect susceptibility to radiation induced endometriosis.

CONCLUSIONS AND RECOMMENDATIONS

Effective radiation protection measures for space crews require both the application of dose limitation and the ability to assess quantitatively the risk of potentially hazardous activities. Limits assure that risk remains within tolerance when doses can be forecast with reasonable certainty. This has value in planning crew rotations and redeployment as well as maximum career exposures. The data from our experimental animal studies, together with human cancer incidence figures compiled by the NAS-BIER /15/ and with new estimates of the doses at Hiroshima and Nagasaki /16/, argue for lowering the individual career bone marrow exposure limit in males from 400 to 200 rem (Table 3). Interim doses should also be scaled down, because experience by NASA has shown that astronaut careers may extend to at least ten years instead of the five years assumed by the Space Science Board. Until the relative susceptibility of human and monkey females to radiation induced endometriosis can be established, we recommend that the maximum career cumulative dose for radiation--of sufficient energy to penetrate the uterus--not be allowed to exceed 25 rem.

TABLE 3 The USAF School of Aerospace Medicine recommendations for radiation dose limits in non-emergency military space operations (male crew members only)

DAILY AVERAGE	.01**
MONTH	10
QUARTER	15
YEAR	25
CAREER*	200

* RELATIVE CANCER RISK: 1.0 - 1.6.
LIFE EXPECTANCY LOSS: 10-25 MONTHS

**SURFACE DOSE IN AIR (RAD)
CNS AND BLOOD FORMING ORGAN EXPOSURE

In some critical missions, risk assessment may be the only option. According to experimental data, both life shortening and cancer risk can be estimated if accurate information on the type, energy, dose, and dose rate is known. Life expectancy loss provides a means for assessing radiation risk relative to other environmental hazards. Within the dose range of 50-800 rad, total body surface radiation, an average life expectancy loss from all types of space radiation has been found to be 2 to 5 monkey-days or 5 to 12.5 person-days per rad. Assuming a 200-rem career exposure and ignoring dose rate effects for a "worst case" estimate this translates to an average life expectancy loss of 1000 to 2000 days. Equivalent non-radiation hazards are: being a coal miner (1100 days); being 30% overweight (1300 days); and having heart disease (2100 days). The risk is less than that of a cigarette-smoking male (2250 days), but greater than that of a cigarette-smoking female (800 days) /10/.

The association of brain tumors with Bragg effect protons emphasizes the importance of accurate determination of the type and linear energy transfer spectrum of the radiation in assessing the risk of delayed effects. These measurements are also important in evaluating the threat from the heavy ion component of galactic cosmic radiation. The lack of information on the physiological and behavioral effects of heavy ions is a major void in our understanding of the space radiation threat. When the contribution of these heavy ions to the radiation environment is determined, realistic ground-based simulations can be conducted to evaluate their potential for undesirable late effects.

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REFERENCES

1. G.V. Dalrymple, I.R. Linday, J.J. Ghidoni, H. Kundel, E.T. Still, R. Jacobs, and I.L. Morgan, Radiat. Res. 28, 406 (1966)

2. G.V. Dalrymple, I.R. Linday, J.J. Ghidoni, J.D. Hall, J.C. Mitchell, H.L. Kundel, and I.L. Morgan, Radiat. Res. 28, 471 (1966)

3. G.V. Dalrymple, I.R. Lindsay, J.J. Ghidoni, J.C. Mitchell, and I.L. Morgan, Radiat. Res. 28, 507 (1966)

4. I.R. Lindsay, G.V. Dalrymple, J.J. Ghidoni, J.C. Mitchell, and I.L. Morgan, Radiat. Res. 28, 446 (1966)

5. A.M. Siegal, H.W. Casey, R.W. Bowman, and J.E. Traynor, Blood 32, 989 (1968)

6. H.W. Casey, P.S. Coogan, and J.E. Traynor, Radiat. Res. 39, 634 (1969)

7. J.E. Traynor and H.W. Casey, Radiat. Res. 47, 143 (1971)

8. J.H. Krupp, Radiat. Res. 67, 244 (1976)

9. M.G. Yochmowitz, D.H. Wood, and Y.L. Salmon, Radiat. Res. 102, 14 (1985)

10. B.L. Cohen and I. Lee, Health Physics 36, 707 (1979)

11. D.H. Wood, M.G. Yochmowitz, Y.L. Salmon, R.L. Boster, and R.L. Eason, Aviat. Space Environ. Med. 54, 718 (1983)

12. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), U. N. Publication E. 77, ix, 1 (1977)

13. Space Science Board, Radiation Protection Guides and Constraints for Space-Mission and Vehicle-Design Nuclear Systems, National Academy of Sciences, Washington, DC (1970)

14. W.K. Sinclair, Adv. Space Res. 3, #8, 151 (1983)

15. National Research Council, Report of the *Committee on the Biological Effects of Ionizing* Radiation: The Effects on Populations of Exposure to Low Levels of Ionizing Radiation (BEIR Report), National Academy of Sciences, Washington, DC (1980)

16. U.S. Department of Energy, Reevaluation of the Dosimetric Factors, Hiroshima and Nagasaki, DOE Symposium Series 55, DOE Technical Information Center, Washington, DC (1982)